HAND DELIVER

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Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Dear Sir/Madam

Re: Docket No. 98P-0434/PSA 1

Berlex Laboratories, Inc. (Berlex) and 3M Pharmaceuticals, a division of Minnesota Mining & Manufacturing Company (3M) submit this supplement to our June 12, 1998 citizen petition, which requested the Food and Drug Administration (FDA) to establish approval standards for generic estradiol transdermal drug delivery (TDD) products before approving the abbreviated new drug application (ANDA) for an estradiol TDD submitted by Bertek Pharmaceuticals, Inc. or any other ANDA applicant. This document serves to supplement the petition with Chemistry, Manufacturing and Control (CMC) issues that are congruent with and further support the arguments put forth already.

The action requested is that no new estradiol TDD product be approved until sufficient evaluation of the CMC information has been completed for safety and efficacy as outlined in the attached document.

If you have any questions regarding this submission, please contact Sharon Brown or Mary Mathisen.

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98P-0434

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CHEMISTRY, MANUFACTURING AND CONTROL (CMC)
SUPPLEMENT TO CITIZEN PETITION
DOCKET #98P-0434

Estradiol that is in solution within a carrier matrix (with or without excipients) will cross the stratum corneum when applied to the skin. However, the rate of skin transport is influenced by the formulation. Bertek claims not to add excipients to their drug substance or adhesive. Even if nothing is added, the adhesive matrix can serve as a penetration enhancer or adhesion promoter. A penetration enhancer includes anything that promotes better skin flux rates in total (i.e. solubility enhancers, better skin contact, crystallization inhibitors, etc.). The innovator product, CLIMARA®, marketed by Berlex, has been shown to be safe and effective in the therapeutic administration of the active drug substance, 17 β-estradiol, in the proprietary transdermal delivery system designed for this drug. If Bertek is not using the same excipients or adhesives as CLIMARA®, their system is different than CLIMARA®. The safety of their adhesive in combination with the drug substance must be evaluated, as well as the efficacy of their system.

There are two major issues associated with the Food and Drug Administration (FDA) review and approval of a generic estradiol TDD product: (1) transdermal products are not simple dosage forms as in the case with immediate release tablets or capsules; a true demonstration of product equivalence is much more challenging and harder to show, and (2) the FDA should be held accountable to define publicly, explicitly, and consistently the specific requirements that Bertek, or any other proposed generic manufacturer of this product, must satisfy to demonstrate such equivalence.

CMC requirements for an ANDA, outlined in Section 314.94(a)(9)(i), covering generic products, including transdermals, are the same for a New Drug Application (NDA), outlined in Section 314.50(d)(1), covering the innovators' products, such as, transdermals (except for some minor additional requirements). The burden is on the generic applicant to show comprehensive technical data in their ANDA that the chemistry, manufacturing and controls of the complete transdermal product are acceptable on their own merits rather than relying on a general reference to the merits of the technical data provided by the innovator in the original NDA. Specifically, the drug product that the ANDA applicant would have to describe completely includes the estradiol active drug substance, all formulation excipients, patch components (adhesives, skin penetration enhancers, laminates, backings, liners, membranes), and non-product contact external container/closure systems. In addition, CMC - related physical/chemical adhesion properties and other U.S.P. testing requirements are real issues that need to be addressed, as they can be anticipated to affect the clinical performance of the estradiol transdermal system.

Section 314.94(a)(9) provides that an ANDA may have different inactive ingredients than the reference listed drug as long as the applicant identifies and characterizes the inactive ingredients in the proposed drug product and provides information demonstrating that the inactive ingredients do not affect the safety of the drug product. The proposed rule published in the November 19, 1998, Federal Register would amend current Section 314.94(a)(9) to recognize the

possibility that the use of different inactive ingredients may also affect the products efficacy. (This constitutes a safety issue as well.).

Section 314.94(a)(9)(v) addresses inactive ingredient changes permitted in drug products intended for topical use. A similar burden of demonstration by an ANDA applicant for a transdermal product to that of an ANDA applicant for a topical product should be in force. That is, a generic transdermal system should contain the same inactive ingredients, qualitatively and quantitatively, as the innovator reference listed drug, to make the equivalence argument work. If the ANDA applicant wanted to use the loophole in this section, that an applicant may seek approval of a drug product that differs from the reference listed drug provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product, then the burden for such demonstration resides with the generic applicant for making the safety argument work.

Potential safety issues associated with the use of different (e.g. formulation ingredients, materials, engineering process, manufacture, controls) estradiol TDD products could arise as a result of the mis-selection of compatible components (particularly critical components controlling the amount, rate and duration of drug delivered), including the additive effects of pharmacologically inactive substances that make up the transdermal system. These dosage forms are relatively complex systems. As listed below, they are composed from a host of diverse materials, many quite complex themselves, which must work in tandem just right or else the intended clinical benefits can be diminished and the safety risks increased. These materials include active drug substance, penetration enhancers, adhesion promoters, backings, drug reservoir (with or without excipients), copolymer membranes, adhesive layers and protective liners. Each of these components must perform adequately. Moreover, the system, as a whole, must deliver the correct amount of drug, at the correct rate, for the correct duration, without unacceptable types and/or levels of impurities/degradants/other substances, for the transdermal product to be safe and to provide the desired clinical benefit.

A review of eleven marketed transdermal products, including that for three estradiol transdermals, CLIMARA® (Berlex), ESTRADERM® (Novartis), and VIVELLE® (Novartis), along with two listed testosterone transdermals, TESTODERM® (Alza) and ANDRODERM® (SmithKline Beecham), reveal an enormous diversity of materials used in the formulation, engineering and manufacture of these products. The following table is a comprehensive listing of all active and the various inactive ingredients included in the drug reservoir/penetration enhancer, the backing material, the copolymer membrane, the drug and/or adhesive layer, and the liner material disclosed in the 1999 Physician's Desk Reference monographs for these eleven products:

Active and Inactive Ingredients of Marketed Transdermal Products[1]

Product	Drug Reservoir/ Penetration Enchancer	Backing	Copolymer Membrane	Drug/Adhesive Layer	Liner
CLIMARA (estradiol)		Translucent polyethylene film		Acrylate adhesive matrix containing estradiol	Protective liner of siliconized or fluoropolymer-coated polyester film attached to the adhesive surface
TESTODERM TTS (testosterone)	Testosterone and alcohol gelled with hydroxypropyl cellulose	Transparent polyester/ethylene-vinyl acetate copolymer film	Ethylene-vinyl acetate copolymer	Polyisobutylene adhesive formulation controlling the rate of testosterone release from the system	Protective liner of silicone-coated polyester covering the adhesive surface
CATAPRES (clonidine)	Clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide	Pigmented, polyester film	Microporous polypropylene membrane that controls the rate delivery of clonidine from the system to the skin surface	Adhesive formulation of clonidine, mineral oil, polyiso-butylene, and colloidal silicon dioxide	Protective slit release liner of polyester that covers the adhesive layer
NITRO-DUR (nitroglycerin)				Nitroglycerin in acrylic-based polymer adhesives with a resinous cross-linking agent to provide a continuous source of active ingredient	Paper, polyethylene-foil pouch
PROSTEP (nicotine)	Nicotine-gel matrix	Backing foil, gelatin and low density polyethylene	Protective foil with well	Beige-colored foam tape and pressure-sensitive acrylate adhesive	Release liner which overlies the adhesive layer
HABITROL (nicotine)		Tan-colored aluminized backing film	Methacrylic acid copolymer solution of nicotine dispersed in a pad of non-woven viscose and cotton	Pressure-sensitive acrylate adhesive	Protective, aluminized release liner which overlays the adhesive layer

Active and Inactive Ingredients of Marketed Transdermal Products[1] (continued)

Product	Drug Reservoir/ Penetration Enchancer	Backing	Copolymer Membrane	Drug/Adhesive Layer	Liner
ESTRADERM (estradiol)	Estradiol and alcohol gelled with hydroxypropyl cellulose	Transparent polyester film	Ethylene-vinyl acetate copolymer	Light mineral oil and polyisobutylene	Protective, siliconized polyethylene terephthalate film attached to the adhesive surface
TRANSDERM-NITRO (nitroglycerin)	Nitroglycerin adsorbed on lactose, colloidal silicon dioxide, and medical fluid	Tan-colored, aluminized plastic backing layer that is impermeable to nitroglycerin	Ethylene-vinyl acetate copolymer	Layer of hypoallergenic silicone adhesive	Protective peel strip
VIVELLE (estradiol)		Translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin		Adhesive formulation containing estradiol, adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3, butylene glycol, styrene-butadiene rubber, oleic acid, lecithin, propylene glycol, bentonite, mineral oil, and dipropylene glycol	Polyester release liner attached to the adhesive surface
DEPONIT (nitroglycerin)		Flexible, flesh-colored, waterproof covering foil		Multilayered adhesive film that constitutes simultaneously the drug reservoir and the release-control system*	Protective aluminum foil attached to the adhesive surface
ANDRODERM (testosterone)	Testosterone, alcohol, glycerin, monooleate, and methyl laurate gelled with an acrylic acid copolymer	Metallized polyester/ethylene-methacrylic acid copolymer/ethyl vinyl acetate backing film	Permeable polyethylene microporous membrane	Peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system; central delivery surface of the system is sealed with a peelable laminate disc	Five-layer laminate containing polyester/polyesterurethane adhesive/aluminum foil/polyesterurethane adhesive polyethylene. The disc is attached to and removed with the release liner; a silicone-coated polyester film

[1]PDR® Electronic Library, 1999, Medical Economics Company, Inc.

Estradiol can be imparted with acceptable performance and stability characteristics if formulated correctly in a suitable dosage form. The pharmacologically inactive substances formulated, engineered and manufactured as a particular type of transdermal system may be intrinsically safe toxicologically when examined alone; however, each of these transdermal products are complex, with each pharmacologically active and inactive component imparting its own effect on the other components, including the estradiol active drug substance, and on the performance of the overall system. These are dynamic processes taking place with a variety of components with a range of potential reactivities. That is the primary reason why all of these approved products were tested comprehensively for physical and chemical compatibility and product stability - to show that over some period of time, at a particular temperature/humidity range, the product will perform adequately in accordance with labeled recommendations. In addition, for products approved under a NDA, safety assessments are made during the clinical development to assure that the whole system, not just the active ingredient is safe and effective. A product approved under an ANDA, using bioequivalence as an assessment of efficacy, will not provide the assurance that the whole system is safe.

The penetration enhancers, adhesion promoters, excipients, vehicles, and the other components of the transdermal dosage form are made up from chemical substances that may be technically referred to as pharmacologically "inactive", but undoubtedly are anything but "inactive" (e.g. unreactive or inert) in a dynamic physical or chemical reactivity sense vis-a-vis opportunities to react with the estradiol, allowing for the potential formation of a number of degradants, including estriol and estrone.

These potential reactions could include physical (active surface, flux, catalytic) effects and/or chemical reactions, including degradation processes, among labile functional groups, which could occur under the right conditions of contact, concentration, moisture, pH, oxygen, or catalysis. The optimum delivery of a particular estradiol transdermal product is very much a function of a particular characterized and controlled analytical profile of the estradiol and its degradants, including the levels of estriol and estrone. It is likely that different analytical profiles will be obtained for this drug product when formulated, engineered and manufactured differently than the innovator drug product; thus, the generic product would be different in key attributes.

The particular analytical profile exhibited for Berlex's CLIMARA® estradiol TDD product is an intrinsic property of this product's safety and efficacy characteristics. A competitor's estradiol TDD product can be expected to be somewhat different, as has been shown. As a result, there could be some likelihood that the safety and efficacy characteristics of the generic product is less favorable than the innovator product. If this would be shown to be true based on the results of careful research and development studies, then a regulatory approval of the generic product, based primarily on bioequivalence attributes, may be inappropriate, and in a worst case scenario, a public health concern.

In summary, there would appear to be a high, but not impossible, set of technical and regulatory standards that must be met by Bertek with their estradiol TDD product, and other potential generic applicants with their versions of this drug product. A simple bioequivalence assessment is not sufficient to assure that generic transdermal products are truly equivalent in the critical safety, efficacy and product performance attributes that the consumer relies upon when they take their medicine. The Bertek estradiol TDD product should be evaluated in consideration of the safety of the drug substance with the adhesive materials and other associated components. CLIMARA® is different from the Bertek product in regards to the lack of excipients used in the Bertek product as well as the composition of the adhesive matrix. The combination of the drug substance with the Bertek adhesion and its associated penetration enhancers has not been evaluated for safety and efficacy. It would be extremely helpful to all concerned in the pharmaceutical industry for the Food and Drug Administration to re-examine this issue, with a full appreciation of its non-trivial complexities, and develop and communicate clear requirements to the Innovative and Generic drug communities to assist them in understanding what needs to be done for these standards to be met. The Agency should recommend that ANDA applicants do the appropriate discriminatory scientific studies in accordance with these guidelines to demonstrate true equivalence between generic and innovative products, so that substitution of one product for the other is valid and appropriate.